Remarks/Arguments

Claims 140, 146-150 have been amended. Claims 140-173 are pending in the application. The following discussion addresses each rejection and objection set forth in the Office Action. No new matter is added by the amendments.

Rejection of Claims 146-150 Under 35 U.S.C. §112, Second Paragraph

Claims 146-150 have been rejected as being unclear in view of the use of the term "substantially." The term has been deleted from Claims 146-150. Withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §102(b)

Examiner rejected Claims 140, 145-147, 149, 151, 156-158, 160, 163-168, 170 and 171 under 35 U.S.C. §102(b) as being anticipated by Radhakrishnan (U.S. patent 5,049,389). The claims are directed to methods of administering epinephrine to the respiratory system of a patient. Applicants have amended the claims to state that the particles are spray-dried and that the tap density of the particles is less than about 0.4 g/cm^3. Radhakrishnan does not teach these limitations and therefore does not anticipate the claims as amended. With respect to the mass mean aerodynamic diameter of the particles, the Examiner asserts that an MMAD of less than 2.1 μm is taught. Radhakrishnan does not actually teach that the dry particles made by his processes possess this feature. At column 16, lines 12-17, the product that has the described MMAD is a mist of aerosolized droplets. Further, products with a low MMAD may not necessarily possess a high fine particle fraction (FPF).

Maa, for example, acknowledges that even very small particles may not deliver efficiently (e.g., possess a high FPF) due to aggregation, for example (see column 2, lines 5-16). Further, as exemplified by the data presented in the specification, a product may have a low MMAD and not possess a high FPF. See Example 9, Table D where products are described that possess an MMAD of less than 3 but have an FPF under 3.4 which is less than 50%.

Finally, Radhakrishnan only generically discloses products which contain epinephrine as part of a very long list of possible active agents that can be formulated. Because the claims require picking and choosing amongst multiple variables (with respect to claim 1, for example, a specified tap density and FPF), the presence of epinephrine in a long list is insufficient to support an anticipation rejection. Indeed, a broad generic disclosure is generally insufficient to defeat the novelty of a claim. See MPEP 2131.02 and the cases cited therein.

The Examiner further rejects Claims 163-168 and 170 stating that the C_{max} and T_{max} of the prior art formulations would be inherently better than what one would expect from a non-intravenous injection of epinephrine. Applicants respectfully disagree. The release profile of a pharmaceutical product relies not only upon the mode of delivery, but the selection of the active agent, the excipients and the product morphology, which, in turn, is impacted by the manner in which the product is made. In this case, the variables that must be selected are too many to conclude that any one epinephrine product, a product which Radhakrishnan did not make, would inherently possess the claimed release profile.

Withdrawal of the rejection is requested.

Rejection Under 35 U.S.C. §103(a)

Claims 140, 145-147, 149, 151, 156-158, 160, 163-168, 170 and 171 have been rejected under 35 USC 103(a) over Radhakrishnan (U.S. patent 5,049,389). For reasons mentioned above, this rejection should also fall. With respect to the assertion that it would have been obvious to improve the FPF of the particles even if the disclosed particles of Radhakrishnan failed to meet this limitation, it is respectfully pointed out that the Examiner has the initial burden of providing a reference which teaches a means of modifying the prior art product or process that would be expected to achieve this improvement.

Claims 140-145, 151, 154-158, 161-168, 170 and 171 have been rejected under 35 USC 103(a) over Maa (U.S. patent 6,284,282) in view of the 56th edition (2002) of the Physicians' Desk Reference. Applicants traverse.

Maa is relied upon to teach powder formulations. Maa is stated to teach formulations that are within the range of 5 to 30 microns, preferably 6-8 microns. Maa particularly teaches the

formulations of *proteins*. The Examiner acknowledges that Maa lacks the teaching of formulations containing epinephrine and sodium tartrate and the administration of said formulations. In addition, although Maa mentioned the use of leucine as an acceptable excipient, Maa does not teach or suggest formulations containing leucine in combination with epinephrine and sodium tartrate. Moreover, even as stated in the reference and as pointed out by the Examiner, spray freeze-drying is a process conceptually similar to spray drying; however they are not the same. Maa further discusses several differences between spray freeze-drying and spray drying and suggests that spray freeze drying produced aerosol powders of very different aerodynamic properties than spray drying powders. The Examiner has provided no evidence which suggests that one would be motivated to modify this essential feature of Maa's process, based on the teachings of Maa. Maa clearly teaches away from the present application. Withdrawal of the rejection is respectfully requested.

Claims 148 and 149 have been rejected under 35 USC 103(a) over Maa (U.S. patent 6,284,282) in view of the Physicians' Desk Reference and further in view of Jakupovic (U.S. Patent 6,221,398). Claims 152, 153, 159 and 169 have been rejected under 35 USC 103(a) over Maa (U.S. patent 6,284,282) in view of the Physicians' Desk Reference and further in view of Warren et al. (*Clin. Pharmacol. Ther.*, 1986, *40(6)*, 673-678). Claims 172 and 173 have been rejected under 35 USC 103(a) over Maa (U.S. patent 6,284,282) and further in view of Adjei (U.S. Patent 6,136,294) and Dorbrozsi (U.S. patent application PG-PUB 2002/0076421). All of the above rejections have used Maa as the primary reference, as applied to independent claim 140. For reasons discussed above, Maa does not teach or suggest the present claims, therefore the Examiner's reliance upon the teachings of the secondary references is rendered moot.

The above notwithstanding, with regard to Jakupovic, there is no motivation to combine the very different processes of the two references. Both references rely upon the process to achieve the products described therein. One would simply not be motivated to combine these teachings.

With respect to Warren et al, the reference does not teach the required amount of epinephrine which would be needed in the formulation of Maa in an administration limited to a single inhalation. Warren's administration of a 3 mg. dose in 30 puffs cannot be extrapolated to an administration of a different epinephrine formulation (which Maa does not teach) because the

peak blood plasma levels achieved will depend not only on the amount of drug in the powder and the number of inhalations achieved but the efficiency of the delivery. Thus, Warren's teachings cannot be meaningfully combined with Maa's to arrive at the present claims.

With respect to Adjei et al. and Dobrozsi and claims 172 and 173, even if one were to conclude that Adjei and Dobrozsi taught that epinephrine and tartaric acid can be combined in a aerosol formulation, the references, alone or in combination with Maa, do not teach the specific combination with leucine in the recited amounts. The Examiner appears to agree that formulations containing 62 to 82% leucine aren't evenly generically disclosed. For example, the Examiner appears to rely upon Adjei's teachings of up to 20% leucine to render obvious the 62% to 82 % leucine limitation. Likewise, the Examiner's appears to rely upon Dobrozsi's teachings of up to 3% carboxylic acid to render obvious the 7 to 17% sodium tartrate limitation. Simply, these teachings miss the mark. Neither do the references teach that compositions having this formulation will possess good to excellent stability and performance, as taught in the specification.

Withdrawal of the rejections is requested.

Double Patenting

Claims 140-143, 145, 151, 154, 159, and 160 have been provisional rejected under the judicially created doctrine of obviousness-type double patenting over US Application 10/818,902 in view of Maa, a patent to which the present application claims priority. For a double patenting rejection to be proper in this case the claims of the two patent applications must be obvious over each other. In determining whether or not the claims are obvious one must look to the claims, not the patent specifications. While it is agreed that the claims of the earlier patent application may dominate the products of the present application, this fact alone does not mandate a double patenting rejection. The claims of the present application are directed to an improved epinephrine formulation that is not specifically described in the claims or patent specification of the '902 application. As discussed above, the broad genus described and claimed in the '902 application (or its related applications and patents) does not render obvious the claimed invention described herein. Withdrawal of the rejection is requested.

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CONCLUSIONS

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

ELMORE PATENT LAW GROUP, PC

By _____
Carolyn S. Elmore
Registration No. 37,567
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

N. Chelmsford, MA 01863
Dated: Jan 4, 2006